

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01N 33/12, 65/00, 43/16, 47/40	A1	(11) International Publication Number: WO 98/21946 (43) International Publication Date: 28 May 1998 (28.05.98)
(21) International Application Number: PCT/US97/20957 (22) International Filing Date: 18 November 1997 (18.11.97) (30) Priority Data: 08/751,590 18 November 1996 (18.11.96) US (71) Applicant: INTERNUTRIA, INC. [US/US]; 550 Cochituate Road, Box 18, Framingham, MA 01701 (US). (72) Inventors: WURTMAN, Judith, J.; Heritage on the Garden, 300 Boylston Street #1205, Boston, MA 02116 (US). LEPENE, Lewis, D.; 40 Battery Street, Townhouse 10, Boston, MA 02109 (US). (74) Agents: VILLACORTA, Gilberto, M. et al.; Pepper Hamilton LLP, 1300 Nineteenth Street, NW, Washington, DC 20036-1685 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITION AND TREATMENT FOR PERSISTENT REPRODUCTIVE TRANSITION SYMPTOMS (57) Abstract The invention relates to compositions and methods of managing the manifestations of the symptoms of persistent reproductive transition (or SPRT). A typical composition contemplated by the invention comprises (i) a first active ingredient comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and (ii) a second active ingredient comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a starch, (b) choline, a source of choline, or combinations thereof, or (c) a combination of (a) and (b). If the second active ingredient of the composition comprises phosphatidyl choline, then the composition contemplated is substantially free of added beta-sitosterol.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

COMPOSITION AND TREATMENT FOR PERSISTENT REPRODUCTIVE TRANSITION SYMPTOMS

1. Field of the Invention

5 The present invention relates to compositions and methods for alleviating ailments symptomatic of premenopausal and/or menopausal disorders, associated in some way with an acute, temporary, developing, or chronic imbalance in the serum levels of endogenous,
10 gynecologically relevant substances, including certain neurotransmitters, neurotransmitter substrates and/or hormones. In particular, the present invention relates to a composition or compositions comprising a mixture of remedial carbohydrates and at least one phytoestrogen,
15 which on administration to a subject in need thereof relieves or manages the disorders, manifestations, conditions, or discomforts complained of.

2. Background of the Invention

20 Somatic, emotional, metabolic and cognitive difficulties, including sleep problems, vasomotor symptoms and mood swings, are just some of the symptoms experienced by many menopausal women and also by many premenopausal or perimenopausal women. The severity of the symptoms
25 caused by these reproductive physiological changes may differ among women of various ages (and even within women of approximately the same age). Some women have little or no discomfort, while others become socially and/or physically dysfunctional. As for women undergoing
30 menopause, fully 58 percent describe the process as "somewhat bothersome", while a third to one fifth of women found it "very bothersome" depending upon the age of the women reaching menopause. Prevention, (Aug. 1994) 78-142. The collection of such various aches, irritability, water
35 retention and other complaints experienced to some degree or another by these women whose bodies are in a state of

flux can be generally referred to as Symptoms of Persistent Reproductive Transition or SPRT.

5 The etiology of these reproductive physiological changes is not universally agreed upon. SPRT-related changes can affect vasomotor, cognitive, psychological and sexual functions. Specific symptoms include, but are not limited to, weight gain, sleep disorders, hot flashes, sweating, nervousness, depression, anxiety, vertigo, fatigue, arthralgia, headache, tachycardia, vaginal dryness and heavy bleeding.

10 It is believed that altered estrogen levels in women may play a significant role in causing SPRT-related ailments. Consequently, Hormonal Replacement Therapy (HRT) has been prescribed as a means to supplement or replace the loss of estrogen commonly observed in women experiencing SPRT-related ailments. The estrogen and endogenous hormones used in HRT, however, have undesirable side effects such as weight gain, excessive bleeding, fluid retention, and increased risk of cancer.

15 See, Prevention, (Aug. 1994) 78-142. Safer and more effective therapies for SPRT-related ailments continue to be sought.

20 There are a number of articles describing the potential treatment of the somatic symptoms of menopausal women by ingestion of foods enriched with phytoestrogens or by ingestion of concentrated forms of phytoestrogens. It has been recognized that the incidence of certain somatic symptoms occurs less frequently in Chinese and Japanese women as compared to women in western countries.

25 Substantial dietary differences exist between these Eastern and Western populations, especially related to the consumption of soy products. Consequently, it has been suggested that the estrogenic effects of phytoestrogens found in soy foods may be responsible for modifying the frequency and severity of somatic symptoms observed in

30

35

menopausal women in different countries. See, Knight, D. C. et al., *Obstetrics & Gynecology*, (1996) 87:897-904.

Phytoestrogens are naturally occurring compounds found in many foods and are defined as plant substances that are structurally or functionally similar to estradiol and consist of a number of classes, including lignans, isoflavones, coumestans and resorcylic acid lignans. Recently, a few reports have appeared purporting to observe the alleviation of some somatic symptoms of menopausal women based on the use of the isoflavonoid class of phytoestrogens. These reports, however, continue to focus solely on the use of isoflavonoids as potential agents for modifying estrogen levels to treat somatic symptoms. Most significantly, these references do not teach, disclose, or suggest any benefits to emotional, cognitive, or metabolic symptoms. Nor do these references teach, disclose, or suggest any benefits to the administration or co-administration of remedial carbohydrates to provide relief to a whole host of SPRT-related ailments.

Descriptions of methods for treating somatic symptoms of menopausal women by the administration of phytoestrogens exist. Gorbach et al., in U.S. Patent No. 5,498,631, describe a method of treating premenstrual symptoms, menopausal symptoms, or a condition related to reduced levels of endogenous estrogen in women by administering isoflavonoids, which are thought to substitute for the reduced levels of endogenous estrogen. Clearly, Gorbach et al. concentrate on the alleged estrogen-like actions of isoflavonoids. Gorbach et al. make no mention of the potential role of isoflavonoids in a composition or treatment, which also includes effective amounts of remedial carbohydrates, to alleviate a broader range of SPRT-related ailments, including those having an etiology in reduced levels of serotonin. Furthermore, Gorbach et al. do not mention the potential role of

phytoestrogens for the treatment of emotional, metabolic, or cognitive disorders.

In U.S. Patent No. 5,506,211 issued to Barnes et al., methods are disclosed for treating patients specifically with the isoflavone genistein to inhibit osteoclastic activity, thereby allegedly preventing osteoporosis. Similarly, Shlyankevich, in U.S. Patent No. 5,424,331, concentrates on the use of phytoestrogens as a means for regulating hormonal levels in women suffering from osteoporosis. Furthermore, Hughes et al., in U.S. Patent No. 5,516,528, describe a composition comprising mammalian estrogen as a means for regulating hormonal imbalances. Neither Shlyankevich nor Hughes et al. disclose a method for alleviating common SPRT-related ailments.

Apart from attempting to treat solely the somatic symptoms related to reproductive physiological changes, other references have utilized chemically modified isoflavones, also referred to herein as phytoestrogen derivatives. In U.S. Patent No. 4,390,559, granted to Zillicken, a composition is described using a chemically modified isoflavonoid-like compounds as antioxidants for the preservation of fats and oils. These methods and compositions do not use the naturally occurring isoflavone. Moreover, the use of excessive amounts of fats and oils would inhibit the beneficial effects of remedial carbohydrates. Similarly, U.S. Patent No. 5,352,384, granted to Shen, describes a modified isoflavone that is combined with a highly insoluble fiber.

In U.S. Patent 4,557,927, granted to Miyake et al., a process is disclosed for enzymatically converting natural soybean glycosides to an alpha-glycosylated product in which the carbohydrate enzyme substrate is covalently bonded to the phytoestrogen. Similarly, isoflavonoid compounds can be synthesized which resemble the natural isoflavones. In Patent Nos. 4,166,862, 4,163,746, 3,949,085 and 3,864,362, granted to Feuer et

al., non-natural isoflavone compounds are synthesized for use as anabolic or catabolic feed additives. Stadler nee Szoke et al., in U.S. Patent Nos. 5,043,326 and 4,826,963, describe a method for the preparation of inclusion complexes of ipriflavon cyclodextrin.

Despite a great deal of effort in developing treatments for menopause, there remains an unfulfilled need for a more effective, comprehensive therapy. In particular, prior compositions for treating menopause have involved the use of hormonal replacement therapy, which fall well short of addressing the needs of those women experiencing SPRT-related ailments. Quite surprisingly, it has now been found that a more general sense of well-being, as well as other benefits, is observed through a regimen that affects the imbalances in the body, which imbalances are due not only to hormone or hormone-like substances but also to other substances of gynecological significance, including classes of neurotransmitters.

In mammals, the amino acid tryptophan is the precursor to serotonin synthesis in the brain. Certain carbohydrates, when ingested, can increase the ratio of tryptophan to large neutral amino acids (T:LNAA) in the blood stream. An increase in the ratio of T:LNAA has been shown to result in a higher level of tryptophan in the brain. A higher level of tryptophan in the brain is believed, in turn, to lead to an increase in the synthesis of endogenous serotonin. While conventional foods (e.g., a potato or a bagel) may fortuitously shift the T:LNAA ratio to a limited extent, these conventional foods also contain fats, sources of protein, other fibers, or may be consumed with other foods that serve as sources of these other components. These other components of conventional foods may slow down digestion, absorption, metabolism and excretion, increase the levels of large neutral amino acids, or otherwise interfere with the desired shift in the balance of specific amino acids in the blood.

It is also important to point out that while a deficiency or imbalance in serotonin levels has emerged as a leading theory behind the symptoms of premenstrual syndrome or PMS (e.g., a number of studies have shown that women with PMS may have a lower serotonin level than women without PMS), such a theory fails to account for or predict the effect of the regulation of serotonin levels (or the levels of other select neurotransmitters, such as dopamine) on premenopausal or menopausal women.

The present invention relates to the discovery that a composition comprising an effective amount of at least one phytoestrogen, in conjunction with a mixture or blend of remedial carbohydrates or in conjunction with choline or a source of choline, can alleviate, treat, or prevent SPRT-related ailments.

3. Summary of the Invention

The present invention is directed generally to compositions exhibiting surprising efficacy in alleviating conditions and/or disorders of the type that women experiencing symptoms of persistent reproductive transition (SPRT) complain of. The present invention is also directed to methods of treating, preventing, inhibiting, managing, ameliorating, or alleviating such symptoms. In particular, relief from the negative effects of the symptoms or manifestations, including somatic, emotional, metabolic, or cognitive disorders, may be achieved through dietary management using the compositions and methods of the invention.

Accordingly, the invention provides a composition for alleviating symptoms of persistent reproductive transition (SPRT) comprising (i) a first active ingredient comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and (ii) a second active ingredient comprising (a) a mixture of remedial carbohydrates including at least one simple remedial

carbohydrate, at least one complex remedial carbohydrate and at least a starch, (b) choline, a source of choline, or combinations thereof, or (c) both (a) and (b), the composition being substantially free of added beta-sitosterol if the second active ingredient comprises phosphatidyl choline. In other embodiments, however, particularly those in which the second active ingredient does not comprise phosphatidyl choline, phytosterols may be added to advantage.

The invention also provides a method of alleviating the negative effects of symptoms of persistent reproductive transition (SPRT) comprising administering to a subject in need thereof an effective amount of at least a first substance comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and an effective amount of at least a second substance comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch, (b) choline, a source of choline, or combinations thereof, or (c) a combination of (a) and (b). Consistent with a method of dietary management, first, second, or both substances are preferably administered with a carrier, more preferably a nutritionally acceptable carrier, most preferably an edible solid, edible semi-solid, or edible liquid carrier.

The invention also contemplates a method that alleviates the negative effects of symptoms of persistent reproductive transition (SPRT) relating to emotional disorders, metabolic disorders, cognitive disorders, or combinations thereof, but not somatic disorders, comprising administering to the subject in need thereof an effective amount of at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof. In a particular embodiment, the method contemplated further comprises administering an effective

amount of a blend of two or more remedial carbohydrates, preferably a mixture of at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch. More preferably, the method further comprises administering an effective amount of choline or a source thereof. Any route of administration can be taken. However, the oral (by mouth) or topical (transdermally, intravaginally, or the like) route is preferred. Moreover, each active component can be administered sequentially, preferably within about an hour of each other, or substantially concurrently.

It has surprisingly been discovered that the compositions and methods of the invention provide great benefits to women who experience a whole range of discomforts associated with SPRT. Such benefits include relief from, for example, somatic, emotional, metabolic, or cognitive associated ailments. It is believed that the compositions and methods of the invention provide relief from the symptoms by supplying particular nutrients, including a combination of selected substances, having the capacity to correct (through a regimen of dietary management) adverse physiological, psychological and psychiatric states stemming from alterations primarily in endocrine synthesis and secretion accompanying a woman's approach, progression and passage through a post reproductive stage during her later years of life.

To name some of the specific benefits observed from the administration of the compositions or implementation of the methods of the invention to subjects suffering from SPRT-related ailments include, but are not limited to, inhibition of breakthrough bleeding, elimination of need for concurrent hormone replacement therapy, stimulation of osteoblastic activity and inhibition of the hardening of the vasculature. In other instances, it has also been observed that subjects receiving treatment experience an improvement in mood, less water retention, less

irritability, or an increased ability to concentrate or remain mentally alert.

Hence, in a specific embodiment of the invention, a useful composition is disclosed for the dietary management of SPRT-related ailments, comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and a mixture or blend of remedial carbohydrates. In another embodiment, the composition of the invention further comprises an amount of choline sufficient to inhibit or reverse episodes of cognitive deficit or decline, including lack of alertness or an inability to maintain premenopausal functionality, in those females unsettled by symptoms of persistent reproductive transition.

In still another embodiment, a composition is described which comprises a combination of at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and an effective amount of choline, a source of choline, or combinations thereof, independent of the presence of an effective amount of a mixture or blend of selected remedial carbohydrates.

Hence, the invention contemplates methods of using therapeutic and/or nutritional compositions for alleviating, treating, preventing, ameliorating, or managing the adverse effects of SPRT-related ailments. Broadly, such methods comprise administering a therapeutically or nutritionally effective amount of the composition to subjects in need thereof.

Other objects of the invention will become apparent to those of ordinary skill in the art upon further consideration of the entire disclosure provided herewith.

4. Glossary of Terms

The following terms appear in the present specification and are defined as follows:

Symptoms of Persistent Reproductive Transition or SPRT - A collection of symptoms, manifestations, disorders, complaints, discomforts, or aches and pains which is experienced by perimenopausal or premenopausal women, menopausal women, or postmenopausal women. In particular, a subject suffering from SPRT or an SPRT-related ailment is a woman having at least one, preferably at least two, most preferably at least three of the symptoms listed in Table 1, below, which symptoms are categorized as somatic, emotional, metabolic, cognitive, or nighttime symptoms.

TABLE 1. ILLUSTRATIVE
DISORDERS/SYMPTOMS/MANIFESTATIONS ASSOCIATED WITH SPRT

<u>I. Somatic</u>	
5	vaginal dryness
	hot flashes
	fluid retention
	breakthrough bleeding
	excessive bleeding
10	vertigo
	headache or migraines
	tachycardia
	libido changes (loss of sexual drive)
	sleep problems
15	joint pain
	frequent urination (incontinence)
	breast tenderness
	chills
	cold sweats (night sweats)
20	
<u>II. Emotional</u>	
	irritability
	anxiety
	lack of energy (lethargic)
25	fatigue
	mood changes (depressed mood, mood swings)
<u>III. Metabolic</u>	
	weight gain
30	marked change in appetite (increased or decreased)
	arthralgia (muscle ache)
	carbohydrate craving
	greater tendency to incur a bone fracture
35	
<u>IV. Cognitive</u>	
	forgetfulness
	recall or short term memory loss
	loss of alertness
	inability to concentrate
40	
<u>V. Nighttime or Sleep Related Symptoms</u>	
	vaginal dryness
	libido change
	sleep problems
45	chills
	incontinence (bladder control)
	night sweats

50 The sub-category of sleep problems may relate to difficulty in initially falling asleep, waking up one or more times during the night, difficulty in falling back asleep once awakening during the night, lack of quality

sleep (e.g., a fitful sleep), a feeling of grogginess in the morning, and the like.

Another subject in need of treatment, who may benefit from the invention, is a woman having episodic or chronic
5 manifestations of at least two of the recited SPRT-related conditions (ailments, disorders and the like) and who is also experiencing changes or irregularities in her menstrual flow or cycle attributable to perimenopausal, menopausal, or postmenopausal transition. It is important
10 to note, however, that some of the same symptoms, which are listed in Table 1, can be induced through the administration of, intake of, or exposure to pharmacological agents, chemicals, hormones and the like, or through accident, trauma, or surgery (e.g., loss or
15 removal of some portion of the reproductive system, such as the uterus and/or one or both ovaries).

Remedial carbohydrates - Simple or complex carbohydrates, including certain forms of starch, which are rapidly digestible and which on consumption increases
20 serotonin levels in the blood, serum, plasma, or synaptic structure(s) relative to the levels of this substance in the blood, serum, plasma, or synaptic structure(s) prior to the consumption of the remedial carbohydrate. That is, consumption of these remedial carbohydrates increases the
25 level of endogenous serotonin synthesis. Examples of such remedial carbohydrates include, but are not limited to, dextrose, galactose, mannose, dextrin, maltodextrin, cyclodextrin, potato starch, pre-gelatinized starch, gelatinized starch, fructose, sucrose, maltose, maltotriose, maltotetraose, or mixtures thereof. It
30 should be pointed out that the remedial carbohydrates, which are suitable for use in the invention, are substances, naturally derived or otherwise, which are deliberately added (as an admixture) to the other
35 components of the compositions of the present invention. That is, carbohydrates, such as conventional flour, that

may be naturally present in certain foodstuffs are not considered to be remedial carbohydrates. In addition, a mixture or blend of two or more, perhaps three or more, remedial carbohydrates refers to a physical combination or admixture of two, three, or more distinct types of remedial carbohydrates. In preferred embodiments of the invention, a mixture comprising at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch may be utilized.

Phytoestrogens - Substances that belong to a family of compounds that are naturally found in certain plants (a natural source), including foodstuffs, especially soy and soy products. Soy proteins are a convenient source of phytoestrogens, especially soy phytoestrogens. Examples of phytoestrogen compounds include, but are not limited to, lignan, genistein, daidzein, Biochanin A, formononetin, O-desmethylangolensin, glycitein, texasin, equol, prunetin, apegenin, coumestrol, saponaretin, 7-hydroxyisoflavone, 5,7-dihydroxyisoflavone, 7,4-dihydroxyflavone, 6,7,4'-trihydroxyisoflavone, or their natural glycosylated (e.g., genistein 7-D-glucoside), acetylated, or methoxylated (e.g., genistein 4'-methyl ether) forms. Phytoestrogens can occur and be used either as the aglycon (i.e., minus the sugar moiety), ester, ether, or as the glycosylated form (i.e., glycosides). Examples, of phytoestrogen glycosides include, but are not limited to, genistin, daidzin, glycitein, saponarin and the like. Naturally obtained phytoestrogens can, of course, be prepared synthetically or semi-synthetically using conventional synthetic methods. In keeping with the desire to substantially utilize only naturally occurring active components, phytoestrogens, as used herein, do not include synthetic derivatives or analogs of the naturally obtained phytoestrogens, except as mentioned above. Such

derivatives or analogs of phytoestrogens may also be referred to herein simply as "phytoestrogen derivatives."

Choline or a Source of Choline - These terms refer to the substance choline or 2-hydroxy-N,N,N-trimethylethanaminium [$\text{HOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$], to choline salts, typically as its halide (e.g., fluoride, chloride, bromide or iodide) or hydroxide salt, or to a substance, which when broken down in the body increases circulating levels of choline. Examples of substances that provides a source of choline in vivo, include but are not limited to citicoline or CDP-choline, phosphatidyl choline and the like. Certain foods or foodstuffs may also provide a source of choline, including but not limited to, animal and plant products, such as bile, brains, lecithin and the like, egg yolks, hops, barley, belladonna, or strophanthus.

Phytosterols - Substances having a steroidal backbone or nucleus and which may be isolated from plants. An example, includes alpha-sitosterol, beta-sitosterol, gamma-sitosterol, campesterol, stigmasterol, delta-5-avenasterol, delta-7-stigmasterol, brassicasterol, lupenol, alpha-spinasterol, or the like. Phytosterols may be present naturally in certain foods and foodstuffs, which may form part of the compositions of the present invention. Phytosterols may also be deliberately added, except as noted above concerning the proviso against a combination of beta-sitosterol and phosphatidyl choline.

5. Detailed Description of the Preferred Embodiments

One of the principal ingredients of the instant compositions, phytoestrogens, is generally available as isoflavones and can be obtained from soy proteins, soybeans, vegetable protein, tempeh, tofu, miso, aburage, atuage, or koridofu. Preferred phytoestrogens include, but are not limited to, genistein, daidzein, glycerin or a combination thereof. As mentioned above, the remedial

carbohydrate mixture or blend constitutes an admixture of two or more, preferably three or more, different types of remedial carbohydrates. Preferred types of remedial carbohydrates include, but are not limited to, dextrose, dextrin, maltodextrin, mannose, pre-gelatinized starch, gelatinized starch and starch, particularly potato starch. Choline or a source thereof can be obtained from any combination of lecithin, choline chloride, choline bitartrate and choline dihydrocitrae. Choline, itself, comprises free choline, its salt, ester, acid, or synthetic or natural conjugate (e.g., CDP-choline, phosphatidyl choline and the like).

In one embodiment of the invention compositions are provided which comprise at least one phytoestrogen in an admixture with at least a second active component selected from (i) a mixture or blend of remedial carbohydrates, (ii) choline or a source thereof, or (iii) both carbohydrates and choline. A preferred composition comprises an admixture of (a) about 20-100 g of soy protein (preferably, about 20-80 g or more preferably, about 30-60 g) comprising about 20-55 mg, preferably about 30-45 mg, of soy isoflavones (i.e., one or more phytoestrogens), (b) about 20-80 g of the remedial carbohydrate mixture or blend comprising about 25-45% of dextrose, about 40-70% of maltodextrin and about 1-10% of potato starch by weight of total remedial carbohydrate, and (c) about 0-5 g of choline, preferably about 1-3 g. A more preferred composition comprises an admixture of (a) about 60 g of soy protein comprising at least about 14 to about 27 mg of genistein and at least about 12 to about 18 mg of daidzein, (b) about 50 g of a remedial carbohydrate mix comprising about 37% of dextrose, about 60% of maltodextrin and about 3% of potato starch by weight of total remedial carbohydrate, and (c) about 1 g of free choline. As discussed above, the genistein and

daidzein can be replaced by genistin and daidzin, either individually or together.

Preferably, the compositions provided are combined with a carrier, more preferably a nutritionally acceptable carrier, such as an edible solid, semi-solid, or liquid carrier, including in the form of dietary product, food, food snacks, or drink, to name a few. Preferred carriers may include sorbet, sherbet, apple sauce, or pudding. Hence, the compositions contemplated can come in many forms including, but not limited to, a dry powder, liquid concentrate, ready-to-drink, ready-to-eat, cold, ambient, hot, beverage or prepared food, e.g., a flavored drink or breakfast cereal, cereal additive (sprinkled on), pastry or baked goods (pop tart, cookie, biscuit, cracker, coffee cake, muffin), pudding or food bar, frozen product (pop tart, ice cream), cake mix, or spread.

Another embodiment of the invention is directed to a method for managing, treating, alleviating, or preventing emotional, metabolic, or cognitive disorders experienced by premenopausal, menopausal, or postmenopausal women by administering to the subject an effective amount of at least one phytoestrogen. Preferable, the subject in need of such treatment is administered about 30-60 g of soy protein, which includes about 30-45 mg of isoflavones. Most preferably, the subject is administered about 60 g of soy protein which includes about 27 mg of genistein and about 18 mg of daidzein.

When the composition or method of the invention calls for the presence of remedial carbohydrates, simple carbohydrates may be selected from dextrose, galactose, mannose, fructose, sucrose, maltose, or mixtures thereof, while complex remedial carbohydrate may be selected from dextrin, maltodextrin, cyclodextrin, maltotriose, maltotetraose, or mixtures thereof. The remedial starch may be in turn selected from potato starch, pre-

gelatinized starch, gelatinized starch, or mixtures thereof.

5 The subject in need of such treatment is administered the therapeutic, dietary, or nutritional composition once or twice a day, preferably in the morning and/or evening. If the composition is administered more than once a day, the administrations are preferably separated by about four to about fourteen hours, preferably, about six to about twelve hours, more preferably about eight to about ten 10 hours. The regimen may last for only a day, a few days, or it may continue for as long as the symptoms persist (e.g., daily for 365 days of the year). More typically, however, the regimen may last anywhere from a period of about one week, two weeks, three weeks, or four weeks to 15 a period of about one month, two months, three months, four months, five months, six months, or at least a year.

In yet another embodiment of the invention, a method is described for managing, treating, alleviating, or preventing in a subject suffering from a SPRT-related 20 condition, which method comprises administering to the subject in need thereof an effective amount of at least one phytoestrogen and at least a second component selected from (i) a mixture or blend of remedial carbohydrates or (ii) choline or source thereof. A preferred method 25 comprises administering to the subject an admixture of (a) about 100 g of soy protein comprising at least about 50 mg of genistin and about 30 mg of daidzin, (b) about 50 g of a remedial carbohydrate mix comprising about 35-40% of dextrose, about 50-60% of maltodextrin and about 1-5% 30 of potato starch by weight of total remedial carbohydrate, and (c) about 1-2 g of a choline salt.

The ultimate amount of phytoestrogen, carbohydrates, and/or choline administered will ultimately vary depending upon known factors, such as the pharmacodynamic 35 characteristics of the particular agent and its mode and route of administration; the age, health and weight of the

recipient; the nature and extent of the symptoms; the kind of concurrent treatment; and the effect desired.

As stated above, the therapeutic compositions can be prepared in the form of a ready-to-use dietary product or in the form of a dietary product concentrate. Ready-to-use products include, but are not limited to, prepared foods such as a beverage, pastry, baked goods, pudding, food bar, or frozen product. Concentrated forms include, but are not limited to a dry powder, liquid concentrate, cereal additive, cake mix, or spread.

To further illustrate the invention, specific examples are provided herewith.

6. Examples

6.1.A Typical Formulation

An edible composition is prepared from a combination of about 20-140 g (preferably about 40-100 g) of soy proteins, including about 20-90 mg (preferably about 30-55 mg) of naturally present or added isoflavones, and about 20-80 g of a mixture of remedial carbohydrates. Preferred compositions comprises about 60-120 of soy protein, including about 45-90 mg of isoflavones. The total weight of the edible composition can range from about 40 g to about 200 g. The composition contains at least two, preferably at least about three, four, or more different types of remedial carbohydrates selected from dextrose, dextrin, maltodextrin, mannose, gelatinized starch, pre-gelatinized starch, rice starch and potato starch. In addition, the edible composition may contain about 0.5-5 g of choline or a source of choline in place of the remedial carbohydrates or in addition to the remedial carbohydrates.

6.2.A Powder Suitable for Reconstitution to a Beverage

A dry powder is prepared comprising phytoestrogen, carbohydrate mix and choline, as follows: soy proteins (60 g), isoflavones (45 mg, in the form of genistein, 27 mg, and daidzein, 18 mg), carbohydrate mix (50 g, comprised of dextrose, 18.5 g, maltodextrin, 30 g, and starch, 1.5 g), choline (1 g). This powder can be mixed with about 8-24 oz. of water to provide a beverage.

6.3.A Ready-To-Drink Beverage

A flavored beverage is prepared comprising about 8-12 oz. of flavored water mixed with phytoestrogen, carbohydrate blend and choline, as follows: soy proteins (55 g), isoflavones (60 mg, in the form of genistin, 35 mg, and daidzin, 25 mg), carbohydrate blend (60 g, comprised of dextrose, 20 g, maltodextrin, 30 g, and starch, 10 g), choline (1.5 g).

6.4.A Baked Muffin

Baked muffins are prepared by adding to two cups BISQUICK, 1 cup milk, and 1 whole egg, a dry powder comprising phytoestrogen, carbohydrate mix and choline, as follows: soy proteins (60 g), isoflavones (45 mg, in the form of genistein, 27 mg, and daidzein, 18 mg), carbohydrate mixture (50 g, comprised of dextrose, 18.5 g, maltodextrin, 30 g, and starch, 1.5 g), choline (1 g). After blending, the batter is poured into muffin molds and baked in the oven at a temperature of about 300-350 degrees Fahrenheit for about 15-30 minutes.

6.5.A Powder Suitable for Reconstitution to a Beverage

A dry powder is prepared comprising phytoestrogen and choline, as follows: soy proteins (65 g), isoflavones (50 mg, in the form of genistein, 28 mg, and daidzein, 22 mg) and choline chloride (3 g). This powder can be mixed with

about 8-24 oz. of water to provide a beverage providing phytoestrogens and choline.

6.6. Rice Pudding

5 Rice pudding is prepared by adding to two cups rice pudding mix, 1 cup milk, and 1 whole egg, a dry powder comprising phytoestrogen, carbohydrate mixture and choline, as follows: soy proteins (90 g), isoflavones (70 mg, in the form of genistin, 40 mg, and glycerin, 30 mg),
10 carbohydrate mixture (50 g, comprised of mannose, 18.5 g, maltotriose, 30 g, and pre-gelatinized starch, 1.5 g), citicoline (1.5 g). After blending, the smooth batter is poured into paper cups and refrigerated for about 30 minutes to about 1 hour prior to consumption.

6.7. Treatment of Subject No. 1

15 A subject suffering from an emotional, metabolic, or cognitive disorder is given a reconstituted beverage obtained from the powder described in Example 6.5 once a
20 day in the morning or at breakfast time. The daily dosing is continued for approximately 90 days. Improvement in the alleviation of the complained of symptoms is observed after about one month from the start of the regimen. After the three month period, the subject reports complete
25 relief from fatigue, anxiety and bouts of forgetfulness.

6.8. Treatment of Subject No. 2

30 A subject suffering from any one or a combination of SPRT-related conditions is treated by the administration of an admixture of (i) phytoestrogens in the form of 60 g of soy protein containing 45 mg of soy isoflavones (in turn containing 27 mg genistein and 18 mg daidzein); (ii)
35 20-80 g of a mixture of remedial carbohydrate including approximately 25 to 45% of dextrose, 40 to 70% of maltodextrin and 1 to 10% of potato starch; and (iii) approximately 0.5 To 5.0 g of free choline (base) or the

calculated equivalent as a choline salt, ester, acid or synthetic or natural conjugate. The admixture is administered once or twice daily, preferably administered between a 6 to 12 hour period for 365 days per year or as long as symptoms of SPRT persist.

6.9. Treatment of Subject No. 3

A subject suffering from an SPRT-related conditions is given approximately 50 g of remedial carbohydrate blend containing approximately 37% of dextrose, 60% of maltodextrin and 3% of potato starch administered in conjunction with a choline source and phytoestrogen source. The compositions is administered twice a day preferably once in the morning and once in the evening for about six months or as long as the SPRT-related symptoms persist.

6.10. Treatment of Subject No. 4

A subject suffering from vertigo, weight gain and lapses in memory is treated by receiving approximately 1.0 g of free choline administered in conjunction with a remedial carbohydrate blend and phytoestrogen source according to the muffin of Example 6.4. The muffin is administered once a day preferably in the morning at breakfast for 255 days. The subject is symptom free after the treatment period.

Hence, the foregoing examples illustrate the successful management, through the administration of a diet of nutritional supplements, of a wide range of symptoms associated with perimenopausal, menopausal, or postmenopausal ailments experienced by women in their middle to late years of life.

It should be apparent to those of ordinary skill in the art that other embodiments of the invention may be readily contemplated in view of the teachings of the present specification. Such embodiments, although not

specifically disclosed, nevertheless fall within the scope and spirit of the invention. Hence, the invention should not be construed as being limited to the specific embodiments provided, which invention is limited solely
5 by the claims that follow.

WHAT IS CLAIMED IS:

1.A composition for alleviating symptoms of persistent reproductive transition (SPRT) comprising (i) a first active ingredient comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and (ii) a second active ingredient comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a starch, (b) choline, a source of choline, or combinations thereof, or (c) a combination of (a) and (b), said composition being substantially free of added beta-sitosterol if the second active ingredient comprises phosphatidyl choline.

2.The composition of claim 1 which further comprises a nutritionally acceptable carrier.

3.The composition of claim 2 in which said carrier comprises an edible solid carrier.

4.The composition of claim 2 in which said carrier comprises an edible liquid carrier.

5.The composition of claim 1 in which said phytoestrogen comprises a soy phytoestrogen.

6.The composition of claim 1 in which said phytoestrogen is obtained from its natural source or from a synthetic or semi-synthetic process.

7.The composition of claim 5 in which said phytoestrogen is obtained from soybean or a soy product selected from tofu, miso, aburage, atuage, or koridofu.

8.The composition of claim 1 in which said phytoestrogen comprises a lignan, genistein, daidzein, Biochanin A, formononetin, O-desmethylangolensin, glycetein, texasin, equol, prunetin, apegenin, coumestrol,
5 saponaretin, 7-hydroxyisoflavone, 5,7-dihydroxyisoflavone, 7,4-dihydroxyflavone, 6,7,4'-trihydroxyisoflavone, or their natural glycosylated, acetylated, or methoxylated forms.

10 9.The composition of claim 8 in which said phytoestrogen comprises genistin, daidzin, glycerin, or saponarin.

15 10.The composition of claim 1 in which said remedial carbohydrates on consumption increases the level of endogenous serotonin synthesis.

20 11.The composition of claim 1 in which said simple remedial carbohydrate is selected from dextrose, galactose, mannose, fructose, sucrose, maltose, or mixtures thereof.

25 12.The composition of claim 1 in which said complex remedial carbohydrate is selected from dextrin, maltodextrin, cyclodextrin, maltotriose, maltotetraose, or mixtures thereof.

30 13.The composition of claim 1 in which said remedial starch is selected from potato starch, pre-gelatinized starch, gelatinized starch, or mixtures thereof.

35 14.The composition of claim 1 in which the second active ingredient comprises a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a remedial starch.

15.The composition of claim 1 in which the second active ingredient comprises choline, a source of choline, or combinations thereof.

5 16.The composition of claim 1 in which the second active ingredient comprises a blend of three or more remedial carbohydrates and further comprises choline, a source of choline, or a combination thereof.

10 17.The composition of claim 14 which contains about 20 to about 80 g of said remedial carbohydrates.

15 18.The composition of claim 14 in which said mixture of remedial carbohydrates comprises about 25 to about 45% dextrose, about 40 to about 70% maltodextrin and about 1 to about 10% potato starch.

20 19.The composition of claim 17 which contains about 50 g of said remedial carbohydrates comprising about 37% dextrose, about 60% maltodextrin and about 3% potato starch.

25 20.The composition of claim 1 which contains about 20 to about 100 g of soy protein.

 21.The composition of claim 1 which contains about 20 to about 55 mg phytoestrogen.

30 22.The composition of claim 21 in which said phytoestrogen comprises about 14 to about 27 mg of genistein and about 12 to about 18 mg of daidzein.

35 23.A method of alleviating the negative effects of symptoms of persistent reproductive transition (SPRT) comprising administering to a subject in need thereof an effective amount of at least a first substance comprising

at least one phytoestrogen, a source of at least one
phytoestrogen, or combinations thereof and an effective
amount of at least a second substance comprising (a) a
mixture of remedial carbohydrates including at least one
5 simple remedial carbohydrate, at least one complex
remedial carbohydrate and at least one remedial starch,
(b) choline, a source of choline, or combinations thereof,
or (c) both (a) and (b).

10 24. The method of claim 23 in which the first, second,
or both substances are administered with an edible
carrier.

15 25. The method of claim 23 which is administered daily
for a period of about one week, two weeks, three weeks,
or four weeks.

20 26. The method of claim 23 which is administered daily
for a period of about one month, two months, three months,
four months, five months, six months, or at least a year.

27. The method of claim 23 which is administered once
daily.

25 28. The method of claim 23 which is administered twice
daily.

30 29. A method of alleviating the negative effects of
symptoms of persistent reproductive transition (SPRT)
relating to metabolic disorders, cognitive disorders, or
combinations thereof, but not emotional disorders, somatic
disorders, or osteoporosis, comprising administering to
the subject in need thereof an effective amount of at
least one phytoestrogen, a source of at least one
35 phytoestrogen, or combinations thereof.

30.The method of claim 29 which further comprises administering an effective amount of a blend of two or more remedial carbohydrates.

5 31.The method of claim 29 which further comprises administering an effective amount of a mixture comprising at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch.

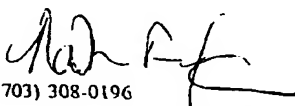
10 32.The method of claim 29 which further comprises administering an effective amount of choline, a source of choline, or combinations thereof.

15 33.The method of claim 29 in which the administration is performed orally.

 34.The method of claim 29 in which the administration is performed topically.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US97/20957

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A01N 33/12, 65/00, 43/16, 47/40 US CL : 514/60, 456, 642, 514 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/60, 456, 642, 514 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched A Modern Herbal Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Extra Sheet.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,331 A (SHLYANKEVICH) 13 JUNE 1995. See whole document.	1-34
Y	US 5,498,631 A (GORBACH et al.) 12 MARCH 1996. See whole document.	1-34
Y	US 3,949,085 A (FEUER et al.) 06 APRIL 1976. See whole document.	1-34
Y	US 4,166,862 A (FEUER et al.) 04 SEPTEMBER 1979. See whole document.	1-34
Y	US 5,516,528 A (HUGHES et al.) 14 MAY 1996. See whole document.	1-34
<input type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art *Z* document member of the same patent family	
Date of the actual completion of the international search 16 JANUARY 1998		Date of mailing of the international search report 10 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer IRENE MARX  Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/20957

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, MEDLINE, AGRICOLA, WPIDS

Search terms: phytoestrogen, estrogen, menopause, PMS, premenstrual, melatonin, genistein, genistin, saponarin, glyectin

